REMARKS

The Examiner has kindly withdrawn several rejections asserted in the previous Office Action. The Examiner, however, has maintained other rejections and we list them here in the order in which they are addressed.

I. Rejections Under 35 USC § 112

A. Claims 40, 42, 44, 46, 50, and 56-58 are rejected under 35 USC § 112 ¶ 1 as allegedly failing to comply with the enablement requirement.

B. Claims 40, 42, 44, 46, 50, 56-58 are rejected under 35 USC § 112 ¶ 2 as allegedly being indefinite.

II. Rejections Under 35 USC § 102(b)

A. Claims 40, 42, 44, 46, 56 & 58 are rejected as allegedly being anticipated by Wu et al., *Proc. Natl. Acad. Sci USA*, 94:13654-13660 (1997)(Wu I).

B. Claims 40, 42, 44, 46, 56, & 58 are rejected as being allegedly anticipated by Wu et al., *Thrombosis Research*, 96:91-98 (1999)(Wu II), as evidenced by Wu I.

C. Claims 40, 42, and 44 are rejected as allegedly being anticipated by Wu II.

D. Claims 40 , 44, and 57 are rejected as allegedly being anticipated by Seegers et al., *Blood*, 5:421-433 (1950).

E. Claims 40, 42, 44, and 57 are rejected as allegedly being anticipated by Vogel et al., *Biochemistry*, 15: 3265-3269 (1976).

F. Claims 40, 42, 44, and 57 are rejected as allegedly being anticipated by Landaburu et al., *Am J. Physiol.*, 193:169-180 (1958).

III. Claims 40, 42, 44, 46, and 56-58 are rejected under 35 USC § 103(a) as allegedly being unpatentable over Wu II in view of Seegers et al.

I The Claims Adhere To 35 U.S.C. § 112

A. The Claims Are Enabled

The Examiner states that:

> ... nothing in the specification indicates that completely carboxylated Gla domain prothrombin was made. ... [and]... the specification does not give guidance for an artisan to arrive at recombinant prothrombin/thrombin that have activity, yet have different structures or characteristics of naturally occurring prothrombin/thrombin encompassed by the claims ...

Office Action pg. 5. The Applicant disagrees. In the present Office Action, the Examiner was apparently unwilling to incorporate by reference the Applicant's persuasive arguments relative to Written Description and apply them to the Enablement rejection.[1] The Applicant's specification contains published references (summarizing the state of the art and properly incorporated by reference) authored by those having ordinary skill in the art describing that post-translational modifications, such as γ-carboxylation, result in an active prothrombin polypeptide.

1. Complete Carboxylation

The Examiner's present postion is that "nothing in the specification indicates that completely carboxylated Gla domain was made". *Office Action pg. 5.* The Applicant disagrees. The Applicant's specification provides specific teachings regarding the carboxylation status of prothrombin:

> GLA-less prothrombin remained bound to the column in the presence of $CaCl_2$. Standard GLA elutes in the presence of $CaCl_2$. Prothrombin in whey from transgenic animals behaves like the normal prothrombin. The results indicate that the transgenic prothrombin is γ-carboxylated like the native molecule.

Applicant's Specification, pg. 49 ln 14-16 [emphasis added]. The Examiner should also note that the Applicant provides complete guidance for one having ordinary skill in the art for constructing and producing transgenic prothrombin from a transgenic animal, for example:

> EXAMPLE 1. Construction of DNAs Useful for Transgenic Expression of Prothrombins in Milk

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[1] The Examiner withdrew the Written Description rejection as a result of this argument.

EXAMPLE 2 Preparation of DNAs for Microinjection.

EXAMPLE 3 Transgenic Animal Production

EXAMPLE 5 Preparation of Milk and Whey

EXAMPLE 4 Assessing Construct Integration

EXAMPLE 6 ELISA Assay of Prothrombin in Milk and Whey of Transgenic Animals

EXAMPLE 7 GLA in Prothrombin Produced in Transgenic Animals

EXAMPLE 8 Chromogenic assay of thrombotic amidolytic activity

EXAMPLE 9 Prothrombin in milk of transgenic mice from embryos injected with WAP6PT1

Applicant's Specification pg 41 ln 4 – pg 54 ln 4. The protocols described in these experiments provide complete guidance for one having ordinary skill in the art to produce a fully-carboxylated recombinant prothrombin protein from a transgenic animal. In particular, Example 8 provides a protocol wherein one having ordinary skill in the art could easily determine prothrombin activity.

2. Guidance For Mutations

The Examine argues that:

> ... the specification does not give guidance for an artisan to arrive at recombinant prothrombin/thrombin that have activity, yet have different structures ...

Office Action pg. 5. The Applicant disagrees and respectfully requests the Examiner to consider the following:

> Certain preferred embodiments ... related to addition, deletion, or alteration of sites to change glycosylation of polypeptides of the invention. Particularly preferred embodiments in this regardr relate to alterations to N-linked glycosylation sites at: Asn-79, Asn-101 and Asn-378, and the Asn-Leu-Ser site at Asn-165 which matches the consensus Asn-X-Ser/Thr sequence of N-linked glycosylation; and other such sites in protrhombins from non-human polypeptides. Such sites are described, for instance, in Degen, *Seminars in Thrombosis and Hemostatsis* 18(2): 230 242 (1992) which is incorporated herein by reference in its entirety, as to the foregoing particularly with regard to glycosylation sites and consensus glycosylation sequences in prothrombins.

Applicant's Specification, pg 24 ln 14-22. This teaching in the Applicant's specification does provide guidance that specific amino acid changes may be made in a prothrombin sequence and still maintain activity. Further, the cited *Degen* reference teaches that prothrombin modifications are not limited to glycosylation sites:

> Both of these regions appear to be flexible in accommodating insertions or deletions and also have a high degree of amino acid substitutions between species.

Degen, pg 231 1st col. 3rd para. Clearly, the Examiner now understands that not only does the Applicant's specification provide guidance that a prothrombin/thrombin polypeptide may have a non-native sequence and maintain activity, but also those having ordinary skill in the art were aware before the application was filed. Nevertheless, the Examiner is reminded that Claim 40 does not recite any element regarding "activity", consequently an enablement rejection on this basis is somewhat questionable.

The Applicant respectfully requests that the Examiner withdraw the present rejection.

B. The Claims Are Definite

1. Claims 40 and 44 Properly Recite "an amino acid sequence"

The Examiner apparently believes that the terms "first and second amino acid sequences" are unclear "... because there are no upper and lower limits *Office Action, pg 7.* The Applicant disagrees. The Examiner has apparently overlooked the modifying language within Claim 40 that specifically provides upper and lower limits: "wherein said first sequence is at least 70% identical to a human prothrombin". Likewise, Claim 44 provides similar language in relation to the term "second amino acid sequence": "wherein said second sequence is at least 80% to 100% identical to that of a mammalian thrombin."[2]

The Examiner is further requested to note that the Applicant has added new dependent Claims 60 & 61 reciting that the first amino acid sequence has "at least 95%" and "at least 100%" identity to a human prothrombin amino acid sequence. *Applicant's Specification pg 9 ln 3-5.* These percents of identity are well accepted to inherently retain the activity of the parent polypeptide. *Revised Interim Written Description Guidelines Training Materials, Example 14, pg 53 (www.uspto.gov/web/offices/pac/writtendesc.pdf)*

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[2] "At least" claim language is properly interpreted as providing a minimum value and (in this case) is extended to a maximum value provided by the complete length of a polypeptide.

The Applicant respectfully requests that the Examiner withdraw the present rejection.

3. Claims 40 & 44 Properly Recite "identical"

The Examiner apparently believes that ".. the term "identical" … could mean two protein sequences … hav[ing] the same domain … [or] … having the same sequence". *Office Action pg 12 ln 6-7.* The Applicant disagrees because one skilled in the art would certainly understand that the context unmistakably refers to the sequence of the amino acids.

Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicant has amended Claim 40 to clarify that the term "identical" refers to a human prothrombin "amino acid sequence", and Claim 44 to clarify that the term "identical" refers to a mammalian thrombin "amino acid sequence".

The Applicant respectfully requests that the Examiner withdraw the present rejection.

II. The Claims Are Not Anticipated

As the Examiner is well aware, a single reference must disclose each limitation of a claim in order for that reference to anticipate the claim. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). This criterion is not met with any of the cited references discussed below.

The Examiner defends the "product by process" doctrine by way of *In re Thorpe,* 227 USPQ 964 (Fed. Cir. 1985) to conclude that a recombinant transgenic prothrombin is anticipated because " … "transgenic" does not impart any patentable structural difference to the protein.". The Applicant disagrees because none of the cited references teach a prothrombin/thrombin protein as defined by the Applicant's present embodiments.

Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicant has amended Claim 40 to recite that the composition further comprises "milk derived from a transgenic mammal". This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicant's business interests, better define one embodiment and expedite the prosecution of this application.

A. Wu I Does Not Anticipate Claims 40, 42,44, 46, 58 & 58

The Examiner states that "Regardless of how prothrombin/thrombin was made, Wu et al. teach fusion prothrombin molecules" *Office Action pg. 9.* The Applicant

disagrees and asserts that the present rejection is moot due to the above amendment to Claim 40.

The Applicant respectfully requests that the Examiner withdraw the present rejection.

B. Wu II Do Not Anticipate Claims 40, 42, and 44

The Examiner states that "Wu II teaches the structural limitations of the prothrombin, regardless of how prothrombin/thrombin was made" *Office Action pg 11.* The Applicant disagrees and asserts that the present rejection is moot due to the above amendment to Claim 40.

The Applicant respectfully requests that the Examiner withdraw the present rejection.

C. Seegers et al. Does Not Anticipate Claims 40, 44, and 57

The Examiner states that "... regardless of how prothrombin/thrombin was made, Seegers et al. teach that prothrombin was isolated from bovine plasma ... [and] ... is completely gamma-carboxylated." *Office Action pg 11.* The Applicant disagrees and asserts that the present rejection is moot due to the above amendment to Claim 40.

The Applicant respectfully request that the Examiner withdraw the present rejection.

D. Vogel et al. Does Not Anticipate Claims 40, 42, 44, and 57

The Examiner states that "... regardless of how prothrombin/thrombin was made, Vogel et al. teach bovine prothrombin... [and] ... is completely gamma-carboxylated". *Office Action pg 12.* The Applicant disagrees and asserts that the present rejection is moot due to the above amendment to Claim 40.

The Applicant respectfully requests that the Examiner withdraw the present rejection.

H. Landaburu et al. Do Not Anticipate The Claims

The Examiner states that "... regardless of how prothrombin/thrombin was made, Landaburu and Seegers teach ... purified bovine prothrombin ... [and] ... is completely gamma-carboxylated". *Office Action pg 22-23* thereby allegedly anticipating the Applicants' claimed embodiments. *Office Action pg 22.* The Applicant disagrees and asserts that the present rejection is moot due to the above amendment to Claim 40.

The Applicant respectfully requests that the Examiner withdraw the present rejection.

III. The Claims Are Not *Prima Facie* Obvious

The Examiner has rejected Claims 40, 42, 44, 46, and 56-58 under 35 USC § 103(a) as allegedly being unpatentable over Wu II in view of Seegers et al. The Applicant disagrees and argues that the Examiner has failed to make a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and *MPEP* § 2142; Establishing A Prima Facie Case Of Obviousness. The Examiner is reminded that if ONLY ONE of the above requirements is not met, then a *prima facie* case of obviousness does not exist. The Applicant rebuts the establishment of a *prima facie* case of obviousness by the argument below.

A. There Is No Motivation To Combine The Teachings Of Wu II And Seegers et al.

The primary difference between Wu II and Seegers et al. is that Wu II teaches the detection and measurement of prothrombin recombinant expression and degradation from mammalian cell culture (i.e., *in situ*), while Seegers et al. attempts to establish parameters for a laboratory diagnostic prothrombin activation assay (i.e., *in vitro*). Wu II does not suggest or provide any motivation that prothrombin activation data, should or could be developed. Seegers et al. does not suggest or provide any motivation that prothrombin should, or could, be expressed in mammalian cell culture as an alternative platform for an activation assay.

Specifically, Wu II is directed towards studying prothrombin glycosylation post-translational modifications following exposure to an anticoagulant (i.e., for example, warfarin). Wu II teaches that warfarin results in expression of rat or human prothrombin that is under-γ-carboxylated. One having ordinary skill in the art would expect an under-γ-carboxylated prothrombin to lack the capability to become activated thereby producing thrombin. Wu II, in fact, contains no discussion whatsoever regarding an *in vitro* diagnostic assay wherein prothrombin activation produces thrombin. If anything, Wu II teaches away from Seegers et al. by stating that prothrombin is converted to thrombin by proteolysis:

> During activation, it [prothrombin] is converted to thrombin by limited proteolysis with factor Xa in complex with cofactor Va ...

Wu II, page 91, col. 2., 1st para. Since Wu II assumes prothrombin activation is occurring under either *in vivo* and/or *in situ* conditions, the need for an elevated sodium citrate concentration is not at issue. Seegers et al., however, is limited to teaching the *in vitro* activation characteristics of bovine prothrombin and makes no mention of any post-translation modifications required for prothrombin activity (i.e., γ-carboxylation or glycosylation) to produce thrombin. Consequently, one having ordinary skill in the art would not be motivated to combine the teachings of Wu II and Seegers et al. because they discuss prothrombins from different species and under different scientific conditions (*i.e., in vivo/in situ versus in vitro*).

The Applicant respectfully requests that the Examiner withdraw the present rejection.

B. Wu II and Seegers et al. Do Not Teach All The Claim Limitations

The Examiner states that:

> Wu et al. teach that rat and human prothrombin were completely gamma-carboxylated (Wu et al. page 95, 1st col., 2nd parag.) ...

Office Action pg 14. The Examiner has apparently misread this paragraph as there is no mention of human prothrombin:

> In an attempt to assess the extent of γ-glutamyl carboxylation in various aglyco-**rFII** fragments by $BaSO_4$ adsorption, it was found that full-length aglyco-**rFII** from vitamin K-treated cells was efficiently adsorbed to $BaSO_4$, indicating complete γ-glutamyl carboxylation in the presence of tunicamycin (data not shown).

Wu II, page 95, 1st col., 2nd para [emphasis added]. The Examiner is requested to note that this paragraph does not mention human prothrombin (i.e., hFII), only rat prothrombin (i.e., rFII). Wu II also cautions that human and rat prothrombin are processed differently:

> It is possible that aglyco-rFII and aglyco-hFII are folded in different conformations ...

Wu II, page 97, 1st col., 2nd para. Clearly, Wu II has not spoken on the issue of human prothrombin γ-carboxylation status and indicates that any inferences from the rat data is unwarranted. Additionally, Seegers et al. makes no mention of prothrombin γ-carboxylation status at all. Finally, neither Wu II nor Seegers et al. teach a composition comprising milk and a prothrombin polypeptide.

The Applicant, therefore, respectfully requests that the Examiner withdraw the present rejection.

C. Wu II And Seegers et al. Do Not Provide Any Expectation Of Success

For the above stated reasons, the Examiner has incorrectly interpreted Wu II as teaching complete γ-carboxylation of human prothrombin. Also discussed above, the differences between the species and scientific objectives of Wu II and Seegers et al. undermine the Examiner's loose conclusion that:

> There would have been a reasonable expectation of success given the Wu et al. for teaching rat and human prothrombins that are completely gamma-carboxylated and is N-glycosylated and Seegers et al. for teaching that prothrombin is activated in the presence of sodium citrate.

Office Action, pg. 14. Clearly, the Examiner fails to meet the "expectation of success" requirement for a *prima facie* case of obviousness because the Federal Circuit has ruled that explicit teachings within the cited references regarding the Applicant's claimed embodiment must be present in order to provide a reasonable expectation of success, for example:

> The expectation of success must come from the prior art and explicitly predict that the process recited in the claims would work.

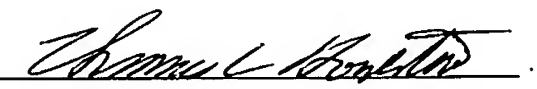
In re O'Farrell, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988) [emphasis added]. While Wu II and Seegers et al. do not meet this criterion from the viewpoint of human prothrombin γ-carboxylation, the Examiner is reminded that the Applicant's present amendment wherein the composition further comprises "milk" is clearly outside the teachings of either Wu II or Seegers et al.

Consequently, the Applicant respectfully requests that the Examiner withdraw the present rejection.

CONCLUSION

The Applicant believes that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicant encourages the Examiner to call the undersigned collect at 617.984.0616.

Dated: January 19, 2007

By: 

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